Therapy With Cortisone

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Two years have elapsed since Hench and associates published their preliminary observations on the use of cortisone in the treatment of rheumatoid arthritis and rheumatic fever. How far have we progressed since then? What is the current status of cortisone as a weapon against disease? What are its limitations?

Response to Cortisone

In this brief period, it has been learned that cortisone is capable of exerting certain fundamental physiological effects associated with increased adrenocortical activity. Among these are: diminution of fibroblastic proliferation; suppression of fever, local inflammatory manifestations, and pain; inhibition of certain allergic processes; increased excretion of potassium; retention of sodium and water; and production of various endocrine dysfunctions.

These findings encouraged many clinical investigators to use cortisone in the treatment of a wide variety of diseases. However, this discussion will be limited to diseases responsive to cortisone therapy and about which opinion seems to have crystallized to some extent. In some disturbances the results have been excellent, even dramatic; in others the effects have been variable, but in some instances the benefits have been transient (see table).

Need More Facts

Although phenomenal advances have already been made in research relating to the chemistry and pharmacology of cortisone and the adrenocorticotropic hormone, ACTH, of the pituitary gland, many large gaps still exist in our knowledge of these hormones. Some of these gaps will be bridged when we have learned more about the following fundamental considerations:

1. The interrelationships of the pituitary, the adrenals, the other endocrine glands, and the various other tissues of the body.
2. The histopathology of the pituitary and adrenal glands of patients with rheumatoid arthritis or other diseases in which cortisone or adrenocorticotropic hormone is effective.
3. The functions of these hormones in normal persons and in patients with rheumatoid arthritis or other diseases known to respond favorably to exogenously administered hormonal agents.
4. The modes of action and interaction of these substances.
5. The metabolism of cortisone—its absorption and fate in the body.

Other Questions Remaining

Certain refinements in our currently available laboratory tests and the development of newer procedures will undoubtedly help us in answering many of the following practical but perplexing questions:

1. How much endogenous cortisone or adrenocorticotropic hormone does a normal person produce daily?

2. How much is produced by persons under stress and how much by patients suffering from diseases benefited by the exogenous administration of these hormones?

3. Do all patients suffering from diseases responsive to cortisone or adrenocorticotropic

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Response to cortisone in various diseases

Beneficial effect often dramatic	Results thus far encouraging	Transient beneficial effects observed
Rheumatoid arthritis	Dermatomyositis	Scleroderma (early)
Still's disease	Psoriasis	Alcoholism
Rheumatoid spondylitis	Retrolental fibroplasia	
Psoriatic arthritis	Agranulocytosis and certain forms of anemia (hemolytic, aplastic, megaloblastic)	**Effects transient, ultimate prognosis unaltered**
Acute rheumatic fever		
Acute lupus erythematosus disseminatus (early or late)	**Results encouraging but may be variable**	Acute leukemia (lymphocytic or granulocytic)
Periarteritis nodosa (early)		Lymphosarcoma
Addison's disease	Acute gouty arthritis	Chronic lymphatic leukemia
Various allergies:	Ulcerative colitis	Multiple myeloma
Bronchial asthma	Regional enteritis	Hodgkin's disease
Hay fever	Nephrotic syndrome	
Angioneurotic edema	Pulmonary granulomatoses:	
Drug sensitization	Sarcoidosis	
Serum sickness	Silicosis	
Exfoliative dermatitis	Berylliosis	
Pemphigus	Purpura hemorrhagica (thrombopenic)	
Inflammatory eye diseases		
Panhypopituitarism		
Adrenogenital syndrome (due to congenital adrenal hyperplasia)		

hormone have inadequate adrenocortical reserve?

4. How much exogenous adrenocorticotropic hormone is required to produce a given amount of cortisone or cortisonelike hormone?

5. What is the time-dose relationship between exogenously administered cortisone or cortisonelike hormone and the amount available in body tissues during a given period?

6. What is the cortisone threshold in the various diseases, and what dose is required to produce beneficial effects without undesirable side reactions?

Thus, it appears that although cortisone is capable of producing excellent—even dramatic—benefits in many patients suffering from diseases which heretofore have proved stubbornly refractory to older methods of treatment, it is quite obvious that a full understanding of the manner in which these substances influence various physiologic or pathologic states remains to be attained. Therefore, until more knowledge of these agents is acquired, we must proceed with caution, accepting calculated risks, in our attempts to develop safe and effective methods for their use.

Undesirable Effects From Cortisone

From our experience to date with cortisone and adrenocorticotropic hormones, we have learned that these agents may at times produce undesirable effects. Therefore, before administering these hormones, the physician should weigh the possibility of producing these effects against the anticipated beneficial results.

A number of relative contraindications to the use of these hormones must be kept in mind. These are of greater or lesser importance, depending upon the nature of the disease (see list). Thus, in general, caution should always

Cortisone therapy—Relative contraindications

Psychotic or prepsychotic personality
Tuberculosis or other serious infections
Congestive heart failure (except that resulting from acute rheumatic carditis)
History of a previous thromboembolic episode
Bacterial or viral infections unless adequate amounts of the proper antibiotics are employed concurrently
Angina pectoris
Duodenal or gastric ulcer
Renal disease
Osteoporosis
Pregnancy
Diabetes mellitus
Hypertension

be exercised with the use of these products in patients having known infection or possessing psychotic tendencies. In the former, these hormones interfere with the immune response and may mask the signs and symptoms of the infectious process; in the latter, a frank psychosis may be precipitated.

The use of cortisone has produced remarkable clinical results in a wide variety of diseases. Even more remarkable is the fact that most of these diseases have heretofore proved unresponsive to other agents. However, even though cortisone is capable of controlling the manifestations of many diseases, its continued use may also produce certain undesirable effects. It cannot be overemphasized that side effects should be considered as evidence of excessive hormonal activity and not as truly toxic effects of the hormone. Moreover, these effects are completely reversible following discontinuation of therapy.

Nevertheless, injudicious use of these potent hormonal agents, like misuse of many commonly employed hormones such as insulin, thyroid substance, or testosterone, may result in certain untoward effects. In the case of cortisone, the physician should respect but not fear the side effects. Dosage has an important bearing on these phenomena. Expressed in simple terms, the problem is to determine the maximum dose compatible with a minimum of undesirable effects. Although much has been learned about the side effects, the problem has not yet been completely resolved.

The Future of Cortisone

Although we are fully cognizant of the therapeutic value of cortisone, this hormone is becoming increasingly more important as an investigative tool in clinical research. We may look upon cortisone as a key which may serve to unlock the door to a better understanding of many disease processes, the mechanism of which still remains obscure. In fact, many of the pages in our textbooks dealing with the etiology, pathogenesis, pathology, diagnosis, and treatment of many conditions may have to be reviewed and rewritten in the light of newly acquired knowledge made possible by clinical and laboratory experiences with cortisone.

One may ask, "What about the future of cortisone as a therapeutic agent?" "How long will it be before we can make categorical statements as to its definitive value in a specific disease?" The answers to these questions will come only after patient and careful study on the part of physicians, public health organizations, and allied professions. This teamwork may also aid in the realization of the greatest of all hopes—the ultimate defeat and eradication of disease.

SUGGESTED READING

(*1*) Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. Preliminary report. Proc. Staff Meet., Mayo Clin. 24: 181–197 (1949); Ann. Rheumat. Dis. 8: 97–104 (1949).

(*2*) Boland, E. W.: Prolonged uninterrupted cortisone therapy in rheumatoid arthritis. Brit. M. J. 2: 191–199 (1951).

(*3*) Gardner, L. I.: Recent advances in therapy with ACTH and cortisone. North Carolina M. J. 12: 41–46 (1951).

(*4*) Derbes, V. J., and Weiss, T.: Untoward actions of cortisone and ACTH. Quart. Rev. Allergy 5: 153–172, 188 (1951).

(*5*) Kass, E. H., and Finland, M.: The role of adrenal steroids in infection and immunity. New England J. Med. 244: 464–470 (1951).

(*6*) Sprague, R. G.: Cortisone and ACTH: A review of certain physiologic effects and their clinical implications. Am. J. Med. 10: 567–594 (1951).

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High Incidence of Measles Reported

The incidence of measles in the United States this season is running far above that for the same periods 1 year ago. The total number of cases reported from September 1, 1951 (the seasonal low week) through January 12, 1952, is 78,085, as compared with 41,128 for the same period a year ago. The median for the 5-year period, 1946–50, is also 41,128. The incidence is concentrated primarily in the eastern part of the country.